

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 April 2002 (04.04.2002)

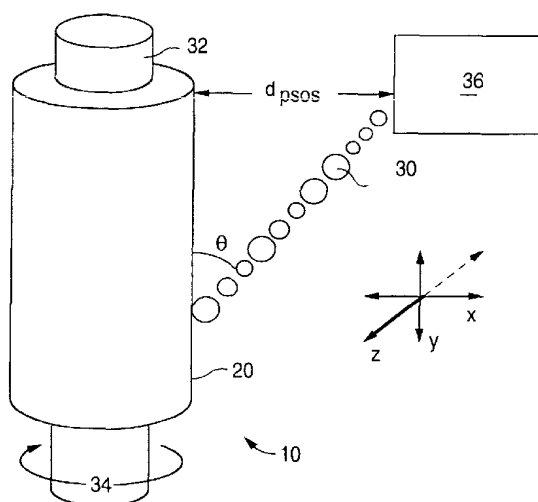
PCT

(10) International Publication Number
WO 02/26162 A2

- (51) International Patent Classification⁷: **A61F 2/06** (74) Agents: **KERRIGAN, Cameron** et al.; Squire, Sanders & Dempsey, L.L.P., 600 Hansen Way, Palo Alto, CA 94304-1043 (US).
- (21) International Application Number: PCT/US01/27627
- (22) International Filing Date:
5 September 2001 (05.09.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/671,759 26 September 2000 (26.09.2000) US
- (71) Applicant: **ADVANCED CARDIOVASCULAR SYSTEMS, INC.** [US/US]; 3200 Lakeside Drive, Santa Clara, CA 95054 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).
- (72) Inventors: **HARISH, Sameer**; 43505 Ocaso Corte, Fremont, CA 94539 (US). **WU, Steven, Z.**; 2299 Lenox Place, Santa Clara, CA 95054 (US).
- Published:**
— without international search report and to be republished upon receipt of that report

[Continued on next page]

(54) Title: A METHOD OF LOADING A SUBSTANCE ONTO AN IMPLANTABLE DEVICE



(57) Abstract: Methods of loading a substance onto an implantable device are disclosed. The implantable device may be a stent or a graft, with or without depots formed within an outer surface thereof. An exemplary method includes the act of projecting particles of the substance from a pressurized particle source onto a preselected region of the implantable device. An implantable device loaded with a substance in accordance with the method is also provided. The projected particles may be made of any substance or substances suitable for loading onto an implantable device in solid form including, but not limited to, therapeutic substances or agents, radioisotopes, radiopaque substances, polymers, proteins, and nucleic acids. Also provided is a method of loading a substance onto a stent having an outer surface with a plurality of depots formed therein. The method includes the act of projecting particles including the substance from a pressurized particle source onto the outer surface of the stent, wherein the particles are loaded into the plurality of depots. A stent loaded with a substance in accordance with the method is also provided.



WO 02/26162 A2



For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

A METHOD OF LOADING A SUBSTANCE ONTO AN IMPLANTABLE DEVICE

BACKGROUND OF THE INVENTION

Field of the Invention

The present invention relates generally to implantable devices, examples of which include stents and grafts. More particularly, the present invention is directed to a method of loading an implantable device with one or more substances.

Description of the Related Art

Percutaneous transluminal coronary angioplasty (PTCA) is a procedure for treating heart disease. A catheter assembly having a balloon portion is introduced percutaneously into the cardiovascular system of a patient via the brachial or femoral artery. The catheter assembly is advanced through the coronary vasculature until the balloon portion is positioned across the occlusive lesion. Once in position across the lesion, the balloon is inflated to a predetermined size to radially compress the atherosclerotic plaque of the lesion against the inner wall of the artery to dilate the lumen. The balloon is then deflated to a smaller profile to allow the catheter to be withdrawn from the patient's vasculature.

A problem associated with the above procedure includes formation of intimal flaps or torn arterial linings which can collapse and occlude the vessel after the balloon is deflated. Moreover, thrombosis and restenosis of the artery may develop over several months after the procedure, which may require another angioplasty procedure or a surgical by-pass operation. To reduce the partial or total occlusion of the artery by the collapse of arterial lining and to reduce the chance of the development of thrombosis and restenosis, an implantable device, examples of which include stents and grafts, may be implanted.

Stents are scaffoldings, usually cylindrical or tubular in shape, which function to physically hold open and, if desired, to expand the wall of the vessel. Typically stents are

capable of being compressed, so that they may be inserted through small cavities via catheters, and then expanded to a larger diameter once they are at the desired location. Examples in patent literature disclosing stents include U.S. Patent No. 4,733,665 issued to Palmaz, U.S. Patent No. 4,800,882 issued to Gianturco, and U.S. Patent No. 4,886,062 issued to Wiktor.

Synthetic vascular grafts are vessel-like configurations that may be positioned into the host blood vessel as a replacement for a diseased or occluded segment that has been removed. Alternatively, a graft may be sutured to the host vessel at each end so as to form a bypass conduit around a diseased or occluded segment of the host vessel.

Although stents and grafts are significant innovations in the treatment of occluded vessels, there remains a need for administering therapeutic substances to the treatment site. Systemic administration of the therapeutic substance often produces adverse or toxic side effects for the patient. Local delivery of therapeutic substances, by contrast, provides a smaller overall dosage that is concentrated at a specific site. Local delivery can produce fewer side effects and achieve more effective results in many cases.

One technique for the local delivery of therapeutic substances is through the use of medicated coatings on implantable devices. A common method for medicating an implantable device involves the use of a polymeric carrier coated onto the surface of the implantable device. A composition is formed by dissolving a therapeutic substance in a solution containing a polymer and a solvent. The composition is applied to the implantable device using conventional techniques, such as spray-coating or dip-coating. The solvent is then removed, leaving on the implantable device surface a coating of the polymer and the therapeutic substance impregnated in the polymer.

A shortcoming of the above-described method is the burst effect, in which an initial rapid release of therapeutic substance upon implantation of the implantable device is followed by a slower, sustained release of therapeutic substance. A higher concentration of therapeutic substance exists at the drying surface, or polymer-air interface, since the therapeutic substance concentrates where the solvent was at the end of the drying process.

Another shortcoming of the above-described method for medicating an implantable device results from the requirement that the therapeutic substance be dissolved in the solvent or

solvent-polymer solution. The amount of therapeutic substance that may be loaded onto the implantable device is limited by the solubility of the therapeutic substance in the solvent or solvent-polymer solution.

Another shortcoming of the above-described method for medicating an implantable device is incompatibility with some therapeutic substances. For example, some therapeutic substances are delicate and cannot tolerate processing in the presence of a solvent and/or a polymer for extended periods of time. This is especially true for peptide-type therapeutic substances, which have tertiary structures susceptible to transmutation.

SUMMARY OF THE INVENTION

The present invention provides a method by which implantable devices, such as stents and grafts, may be loaded with therapeutic substances, among other possibilities, such that the burst effect and the transmutation of delicate therapeutic substances are minimized while loading of the substances is maximized.

An exemplary method within the present invention includes the act of projecting a dry stream of particles including a therapeutic substance from a pressurized particle source onto a preselected region of the implantable device.

In some embodiments, the therapeutic substance is selected from antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergic substances and combinations thereof. In other embodiments, the substance is a radioactive isotope or a radiopaque substance. In still other embodiments, the substance is a bioabsorbable polymer, a biomolecule, or a biostable polymer.

The preselected region upon which the particles are projected may include the entire outer surface or a portion of the implantable device, such as a portion in a middle section of the implantable device or a portion adjacent an end of the implantable device.

In some embodiments, the outer surface of the implantable device includes a plurality of depots formed therein. In such embodiments, particles may be projected onto a portion of the

outer surface and within the depots. The method may additionally include the act of removing the particles from the outer surface such that the particles remain within the depots.

Another exemplary method within the present invention includes the act of applying a polymeric primer to the implantable device prior to the act of projecting particles. In addition, the method may include the act of applying a polymeric topcoat to the implantable device subsequent to the act of projecting particles.

These and other aspects of the present invention may be better appreciated in view of the detailed description and drawings of the exemplary embodiments.

BRIEF DESCRIPTION OF THE DRAWINGS

Figure 1A is a perspective view of an implantable device with a central hollow bore.

Figure 1B is a cross-sectional side view of the implantable device of Figure 1A taken along line 1B-1B of Figure 1A.

Figure 1C is a side view of the implantable device of Figure 1B taken along line 1C-1C of Figure 1B.

Figure 2A is a side view of an exemplary stent formed of thread elements engaged to one another by connecting elements.

Figure 2B is an enlarged view of section 2B of the stent of Figure 2A, wherein the thread elements and connecting elements have depots formed therein.

Figure 2C is a cross-sectional view of a depot of the stent of Figure 2B taken along line 2C-2C of Figure 2B.

Figure 3 illustrates a particle that includes a therapeutic substance.

Figure 4 illustrates a method of projecting particles like that of Figure 3 onto the implantable device of Figure 1A in accordance with one embodiment of the present invention.

Figure 5A illustrates the implantable device of Figure 1C onto which a primer layer has been applied prior to the loading of particles thereon by the method of Figure 4.

Figure 5B illustrates the primed implantable device of Figure 5A, wherein the particles of Figure 3 have adhered to the primer layer.

Figure 5C illustrates the primed implantable device of Figure 5A, wherein the particles of Figure 3 have been embedded in the primer layer.

Figures 6A, 6B, and 6C illustrate various patterns in which the particles of Figure 3 may be loaded onto the outer surface of the implantable device of Figure 1A.

Figure 7A illustrates the stent of Figure 2C, wherein the particles of Figure 3 have been loaded onto the outer surface and within the depot.

Figure 7B illustrates the stent of Figure 7A after surplus particles have been removed from areas other than within the depot.

Figure 8 illustrates the stent of Figure 2C, wherein the particles of Figure 3 have been loaded onto the primed outer surface and within the primed depot.

Figure 9A illustrates the implantable device of Figure 5B after a topcoat has been applied over the particles.

Figure 9B illustrates the implantable device of Figure 7B after a topcoat has been applied over the particles within the depot.

Figure 9C illustrates the implantable device of Figure 7B after a topcoat has been applied along the outer surface and over the particles within the depot.

Figure 9D illustrates the implantable device of Figure 8 after a topcoat has been applied over the particles within the depot and over the particles along the outer surface.

DETAILED DESCRIPTION

The present invention provides methods of loading a substance onto an implantable device, i.e., a device that is designed to be implanted in a human or animal body.

The substance so applied may include any therapeutic substance compatible with the loading methods described below, which involve the projection of a dry stream of particles from a pressurized source onto the surface of the implantable device.

The implantable device may have surface features or treatments that facilitate the loading of the substance onto the implantable device. The present invention provides both effective and economical means for preparing implantable devices that have the capability of delivering therapeutic substances, including substances that are incompatible with conventional methods of loading implantable devices.

Implantable Device

The implantable device used in conjunction with the present invention may be any implantable device, examples of which include self-expandable stents, balloon-expandable stents, and grafts, among other possibilities. The implantable device can be made of a metallic material or an alloy such as, but not limited to, stainless steel, "MP35N," "MP20N," ELASTINITE (Nitinol), tantalum, nickel-titanium alloy, platinum-iridium alloy, gold, magnesium, or combinations thereof. "MP35N" and "MP20N" are trade names for alloys of cobalt, nickel, chromium and molybdenum available from standard Press Steel Co., Jenkintown, PA. "MP35N" consists of 35% cobalt, 35% nickel, 20% chromium, and 10% molybdenum. "MP20N" consists of 50% cobalt, 20% nickel, 20% chromium, and 10% molybdenum. The implantable device may also be made from bioabsorbable or biostable polymers. A polymeric implantable device should be chemically compatible with any substance to be loaded onto the implantable device.

Figures 1A, 1B, and 1C provide views of an exemplary implantable device 10, e.g., a stent or graft. Implantable device 10 is a generally tubular structure that includes a body 12 having a first end 14 and an opposing second end 16. A central hollow bore 18 extends longitudinally through body 12 from first end 14 to second end 16, giving body 12 a thickness t_1 between an outer surface 20 and an inner surface 22. Implantable device 10 can have any suitable length l_1 . The values of length l_1 and thickness t_1 depend, for example, on the procedure for which implantable device 10 is used.

The surface properties of implantable device 10 may vary according to the desired use of implantable device 10. In some embodiments, inner surface 22 and/or outer surface 20 of implantable device 10 is polished via conventional electropolishing techniques, the use of abrasive slurries, or other polishing methods known to those of ordinary skill in the art. In other embodiments, portions of outer surface 20 are roughened via the creation of asperities while inner surface 22 remains smooth. Asperities can be created by projecting a stream of pressurized grit onto outer surface 20. Asperities can also be formed by removing material from outer surface 20, for example, by chemical etching with or without a patterned mask. Alternatively, asperities can be formed by adding material to outer surface 20, for example, by welding powder to outer surface 20 or by sputtering onto outer surface 20.

Figure 2A is a side view of implantable device 10. In Figure 2A, body 12 of implantable device 10 is formed from thread elements 24 engaged to one another by connecting elements 26. However, the underlying structure of implantable device 10 can be of virtually any design.

Figure 2B illustrates the portion of implantable device 10 shown in circle 2B of Figure 2A. Figure 2B shows that thread elements 24 and connecting elements 26 have a plurality of depots 28 formed in outer surface 20. Depots 28, which may also be referred to as pores or cavities, can be formed in virtually any implantable device 10 structure at any preselected location within implantable device 10. The location of depots 28 within implantable device 10 varies according to intended usage and application. Depots 28 may be formed on implantable device 10 by exposing outer surface 20 to an energy discharge from a laser, such as an excimer laser. Alternative methods of forming such depots 28 include, but are not limited to, physical and chemical etching techniques. Such techniques are well-known to one of ordinary skill in the art.

Figure 2C is a cross-sectional view of a single depot 28 of Figure 2B. Depot 28 may have any preselected depth d , width w , and geometrical configuration. Depth d and width w of depot 28 typically depend on the material and dimensions of implantable device 10 and the type and amount of substances deposited within depot 28 as well as on the clinical purpose and usage of implantable device 10. Depth d and width w of the individual depots 28 formed on a single implantable device 10 can vary relative to one another. Depot 28 may be formed in a variety of selected geometrical shapes including, but not limited to, generally cylindrical shapes, generally conical shapes, generally round shapes, elongated trenches, and irregular shapes. As discussed

further below, particles may be deposited into depots 28 and/or along outer surface 20 of implantable device 10.

Substances Applied to the Implantable Device

In accordance with the present invention, particles are projected onto an implantable device, e.g., implantable device 10 of Figures 1A-1C and 2A-2C. The particles may be made of any substance suitable for loading onto implantable device 10 in solid form. Such substances include, but are not limited to, therapeutic substances or agents, radioisotopes, radiopaque substances, polymers, proteins, and nucleic acids.

In addition, a single particle may be made of more than one substance, e.g., a therapeutic substance and a carrier substance. For example, a single particle may include a mixture of at least two different substances. In another embodiment, a single particle includes a first substance and a second substance that covers at least a portion of the first substance so that there may be a timed release of the first substance. In such embodiments, the number, type, and ratio of substances within the particle are treatment-specific. However, the substances within a single particle should be mutually compatible, such that the characteristics, effectiveness, and physical structure of the substances are not adversely altered.

An exemplary particle 30 is illustrated in Figure 3. Typically, particle 30 is rounded or spherical in shape as depicted in Figure 3. However, particle 30 may be of any shape as long as particle 30 is otherwise suitable for use with the present invention.

The size of particle 30 is dependent, in part, on the size of the particular region of implantable device 10 upon which loading of particles 30 is desired. In embodiments in which outer surface 20, in part or in entirety, is to be loaded with particles 30, the diameter d_p of particles 30 can range from about 5 microns to about 20 microns, or more particularly from about 5 microns to about 10 microns. In embodiments in which depot 28 within outer surface 20 is to be loaded with particles 30, however, particles 30 should be no larger than depot 28 itself. More particularly, particles 30 should have a size that not more than about 25% of the size of depot 28.

Particles 30 of suitable size may be made using various conventional techniques known to those of ordinary skill in the art including, but not limited to, micronizing bulk materials.

Alternatively, suitable particles 30 of a particular substance may be obtained from a commercial supplier of that substance and used in the present invention with or without modification. Particles 30, particularly when obtained from a commercial supplier, may include extraneous materials, e.g., fillers such as cellulose, in addition to the substance desired to be loaded onto implantable device 10. Such materials should be biocompatible as well as compatible with the substance to be loaded onto implantable device 10, such that the characteristics, effectiveness, and physical structure of the substance is not adversely altered.

While particles 30 themselves are projected in dry, solid form onto implantable device 10, as will be described below, particles 30 may contain trace amounts of a liquid, such as a solvent used during manufacturing or processing of particles 30. In addition, particles 30 may contain some amount of water, particularly if particle 30 is made of a hygroscopic substance, since such substances absorb moisture from the air.

Therapeutic substances that may be used with the present invention include, but are not limited to, antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, antiallergic, antiangiogenic, and angiogenic substances as well as combinations thereof. Examples of such antineoplastics and/or antimitotics include paclitaxel (e.g., TAXOL by Bristol-Myers Squibb Co., Stamford, Conn.), docetaxel (e.g., TAXOTERE from Aventis S.A., Frankfurt, Germany) methotrexate, azathioprine, vincristine, vinblastine, fluorouracil, doxorubicin hydrochloride (e.g., ADRIAMYCIN from Pharmacia & Upjohn, Peapack N.J.), and mitomycin (e.g., MUTAMYCIN from Bristol-Myers Squibb Co., Stamford, Conn.) Examples of such suitable antiinflammatories include glucocorticoids such as dexamethasone, methylprednisolone, hydrocortisone and betamethasone, superpotent glucocorticoids such as clobetasol, halobetasol, and diflucortolone, and non-steroidal antiinflammatories such as aspirin, indomethacin and ibuprofen. Examples of such antiplatelets, anticoagulants, antifibrin, and antithrombins include sodium heparin, low molecular weight heparins, heparinoids, hirudin, argatroban, forskolin, vapiprost, prostacyclin and prostacyclin analogues, dextran, D-phe-pro-arg-chloromethylketone (synthetic antithrombin), dipyridamole, glycoprotein IIb/IIIa platelet membrane receptor antagonist antibody, recombinant hirudin, and thrombin inhibitors such as ANGIOMAX (Biogen, Inc., Cambridge, Mass.) Examples of such cytostatic or antiproliferative agents include actinomycin D as well as derivatives and analogs thereof (manufactured by Sigma-Aldrich, Milwaukee, WI;

or COSMEGEN available from Merck & Co., Inc., Whitehouse Station, NJ), angiopeptin, angiotensin converting enzyme inhibitors such as captopril (e.g., CAPOTEN and CAPOZIDE from Bristol-Myers Squibb Co., Stamford, Conn.), cilazapril or lisinopril (e.g., PRINIVIL and PRINZIDE from Merck & Co., Inc., Whitehouse Station, NJ); calcium channel blockers (such as nifedipine), colchicine, fibroblast growth factor (FGF) antagonists, fish oil (omega 3-fatty acid), histamine antagonists, lovastatin (an inhibitor of HMG-CoA reductase, a cholesterol lowering drug, brand name MEVACOR from Merck & Co., Inc., Whitehouse Station, NJ), monoclonal antibodies (such as those specific for Platelet-Derived Growth Factor (PDGF) receptors), nitroprusside, phosphodiesterase inhibitors, prostaglandin inhibitors, suramin, serotonin blockers, steroids, thioprotease inhibitors, triazolopyrimidine (a PDGF antagonist), and nitric oxide. An example of an antiallergic agent is permirolast potassium. Examples of antiangiogenic agents include thalidomide and angiostatin. Examples of angiogenic agents include vascular endothelial cell growth factor (VEGF) and fibroblast growth factor (FGF). Examples of arteriogenic agents include histimine, MCP-1, lipo-polysaccharide, and β -FGF. Other therapeutic substances or agents that may be used include alpha-interferon, genetically engineered epithelial cells, and dexamethasone. While the preventative and treatment properties of the foregoing therapeutic substances or agents are well-known to those having ordinary skill in the art, the substances or agents are provided by way of example and are not meant to be limiting. Other therapeutic substances are equally applicable for use with the disclosed methods and compositions.

In other embodiments, the particles may be made of a radioactive isotope or a radiopaque substance. Such substances help to facilitate implantable device usage in radiotherapeutic procedures. Examples of radioactive isotopes include, but are not limited to, phosphoric acid ($\text{H}_3\text{P}^{32}\text{O}_4$), palladium (Pd^{103}), cesium (Cs^{131}), and iodine (I^{125}). An example of a radiopaque substance is gold.

In still other embodiments, the particles may be made of a polymeric material. Suitable polymeric materials include, but are not limited to, bioabsorbable polymers, biomolecules, and biostable polymers. Bioabsorbable polymers are gradually absorbed or eliminated by the body by hydrolysis, metabolic process, bulk, or surface erosion and thus are not present sufficiently long after delivery to cause an adverse local response. Examples of bioabsorbable materials include, but are not limited to, polycaprolactone (PCL), poly-D, L-lactic acid (DL-PLA), poly-L-

lactic acid (L-PLA), poly(lactide-co-glycolide), poly(hydroxybutyrate), poly(hydroxybutyrate-co-valerate), polyorthoester, polyanhydride, poly(glycolic acid), poly(glycolic acid-cotrimethylene carbonate), polyphosphoester, polyphosphoester urethane, poly (amino acids), cyanoacrylates, poly(trimethylene carbonate), poly(iminocarbonate), copoly(ether-esters), polyalkylene oxalates, polyphosphazenes, polyiminocarbonates, and aliphatic polycarbonates. Biomolecules such as heparin, fibrin, fibrinogen, cellulose, starch, and collagen are typically also suitable. A biostable polymer does not break down in the body, and thus a biostable polymer is present in the body for a substantial amount of time after delivery unless some modification is made to allow the polymer to break down. Examples of biostable polymers include, but are not limited to, PARYLENE, PARYLAST, polyurethane (for example, segmented polyurethanes such as BIOSPAN), polyethylene, polyethylene terephthalate, ethylene vinyl acetate, silicone, and polyethylene oxide.

In other embodiments, particles 30 may include nucleic acids or proteins. Examples of such nucleic acids include phosphorodiamidate morpholino oligomers (PMO), cyclic-3'-5'-adenosine monophosphate (8-C1-cAMP), Antisense oligonucleotides, and various nucleic acids encoding for growth factors such as vascular endothelial cell growth factor (VEGF). Examples of proteins include growth factors such as VEGF.

Loading Particles onto an Implantable Device

Prior to projecting particles 30 onto implantable device 10, implantable device 10 should be clean and free from contaminants that may be introduced during manufacturing. Implantable device 10 may optionally be subjected to physical treatments, such as, but not limited to, the creation of depots 28 within outer surface 20 or the polishing of inner surface 22 and/or outer surface 20, as described above.

In embodiments in which inner surface 22 of implantable device 10 has been polished smooth, particular care should be taken to protect inner surface 22 during projection of particles 30 onto outer surface 20. For example, a mandrel or a hypo tube may be inserted within hollow bore 18 of implantable device 10, such that inner surface 22 is shielded from projected particles 30. Alternatively, a balloon may be inserted into hollow bore 18 of implantable device 10 and inflated to prevent particles 30 from striking inner surface 22. Inner surface 22 can also be masked with a temporary protective coating that is removed after particles 30 have been

projected onto outer surface 20 of implantable device 10. By example and not limitation, polyvinyl alcohol (PVA) can be dissolved in water having a temperature of 100°C to form an 80% PVA solution by weight. The PVA solution is applied to inner surface 22 and allowed to dry. After particles 30 have been projected onto outer surface 20, the temporary PVA coating can be removed from inner surface 22 by soaking the coated stent in water.

In Figure 4, implantable device 10 is shown mounted upon a rotatable mandrel 32. Mandrel 32 moves implantable device 10 in a rotational direction 34 while particles 30 are projected at outer surface 20 from a pressurized particle source 36 at an angle θ to a vertical axis y of implantable device 10 and from a distance d_{psos} between particle source 36 and outer surface 20. Particle source 36 is passed along the y axis over outer surface 20 of implantable device 10 as particles 30 are projected at implantable device 10. By way of example and not limitation, pressures from about 10 to about 60 PSI (from about 69 to about 410 kPa) can be used to project particles 30 at the angle θ of 30-90° to vertical axis y and from the distance d_{psos} of approximately 3-10 cm from outer surface 20 of implantable device 10 for approximately 1-3 seconds.

The pressure with which particles 30 are projected from particle source 36 depends, in part, on the size of particles 30 to be projected. Larger particles 30, e.g., 10-20 microns, are typically projected using lower pressures, e.g., 30-60 PSI (210-410 kPa), while smaller particles 30, e.g., 5-10 microns, are typically projected using higher pressures, e.g., 60-90 PSI (410-620 kPa). Regardless of the size of projected particles 30, the pressure at which particles 30 are projected should not be so high as to cause removal of polish or roughening of outer surface 20.

The angle θ to vertical axis y of implantable device 10 is dependent upon the distance d_{psos} between particle source 36 and outer surface 20; the greater the distance d_{psos} , the smaller the angle θ employed. The angle θ is typically in the range from about 30° to about 90°, or more particularly in the range from about 35° to about 45°.

A stream of particles 30 is projected onto outer surface 20 of implantable device 10 in this embodiment. Individual particles 30 within the stream may or may not be of uniform size and shape. Further, individual particles 30 within the stream may or may not be of uniform composition, since individual particles 30 within a stream may be made of the same substance(s) or of different substances.

In some embodiments, mandrel 32 is capable of motion along the x, y, and z axes as well as in the rotational direction 34. Similarly, particle source 36 may be capable of motion along the x, y, and z axes as well as of rotation about implantable device 10, with or without a mandrel inserted therein, in the direction 34.

The method of projecting particles as depicted in Figure 4 and described above may be used to load particles onto a preselected region of implantable device 10 as discussed below.

a. Loading Particles on the Outer Surface of the Implantable Device

In some embodiments, it is desired to load particles 30 along outer surface 20 of implantable device 10. In such embodiments, a polymeric primer 38, may be applied to outer surface 20 of implantable device 10 prior to the projection of particles 30 onto outer surface 20, as depicted in Figure 5A. Primer 38 facilitates retention of particles 30 on outer surface 20. As shown in Figure 5B, particles 30 may adhere to the polymeric material of primer 38 upon impact. Alternatively, particles 30 may become completely or partially embedded in primer 38, as depicted in Figure 5C.

The primer 38 should be biocompatible, including polymers that are non-toxic, non-inflammatory, chemically inert, and substantially non-immunogenic in the applied amounts. Examples of suitable polymers were listed above with reference to polymers of which particle 30 may be made, and such examples are equally applicable here.

Polymeric primer 38 may itself include a therapeutic substance, which may be delivered in combination with the therapeutic substance of particle 30.

Polymeric primer 38 can be applied onto outer surface 20 of implantable device 10 by any conventional method, such as by spraying the polymeric material onto implantable device 10 or immersing implantable device 10 in the polymeric material. Variations of spray and immersion techniques are also suitable methods of applying primer 38 to implantable device 10. In one such variation, primer 38 may be applied by spraying or immersing implantable device 10 as described above. The polymer-coated implantable device 10 is then centrifuged. The rotation of implantable device 10 creates a centrifugal force upon the polymeric material applied to implantable device 10. This centrifugal force causes excess accumulations of the polymer to be more evenly redistributed over implantable device 10 and thus provides a more even, uniform

primer 38 on implantable device 10. The rotational speed during centrifugation can be varied. Higher RPM values may provide improved uniformity and a reduction in defects. However, lower RPM values improve the total loading of the polymeric material onto implantable device 10. Increasing the total centrifugation time may also improve the uniformity and reduce defects in the primer 38 on implantable device 10.

By way of example, and not limitation, the polymeric primer 38 can have a thickness t_2 of about 0.5 microns to about 2.0 microns. The particular thickness t_2 is dependent on the desired use of primer 38 and the type of procedure for which implantable device 10 is employed.

The primer 38 may be dried prior to the projection of particles 30 onto the primer 38. Such drying may be accomplished using conventional methods known to one of ordinary skill in the art using techniques such as, but not limited to, evaporation at ambient pressure and room temperature in an anhydrous atmosphere for up to 48 hours, or exposure to mild heat, e.g., 60-65°C, with or without vacuum.

Once primer 38 has been applied, and optionally dried, particles 30 may be loaded onto the primer-coated outer surface 20. In some embodiments, outer surface 20 of implantable device 10 is completely loaded with particles 30, as depicted in Figure 6A. In such embodiments, the above-described process of projecting particles 30 upon outer surface 20 from particle source 36, as depicted in Figure 4, may be performed in multiple cycles, with implantable device 10 being rotated in rotational direction 34 between cycles. By way of example and not limitation, a first cycle may be performed in which particle source 36 is passed along the y axis over outer surface 20 at a pressure of about 10 PSI (69 kPa) from distance d_{psos} of 10 cm for approximately 3 seconds. Implantable device 10 is then rotated 120° in rotational direction 34, and the process is repeated for two more cycles, in between which implantable device 10 is again rotated 120° in rotational direction 34, thereby loading the entire outer surface 20 with particles 30 as depicted in Figure 6A.

It is important to note that the entire outer surface 20 need not be loaded with particles 30. For example, particles 30 may be projected solely at a middle region 40 of the primered implantable device 10, such that particles 30 are loaded only in middle region 40 of outer surface 20 and are not loaded near to opposing ends 14 and 16 of outer surface 20 as shown in Figure 6B. Alternatively, as shown in Figure 6C, particles 30 may be projected at one or both ends 14

and 16 of outer surface 20 to load particles 30 at one or both ends 14 and 16 of the primed implantable device 10.

b. Loading Particles into Depots Formed in the Outer Surface of the Implantable Device

As mentioned above, some implantable devices may have depots formed in a surface thereof, e.g., Figures 2B and 2C. In such embodiments, it may be desired to load particles 30 solely within the depots 28 of outer surface 20 of implantable device 10. Other than cleaning, implantable device 10 typically requires no particular surface treatment to retain particles 30 within depots 28.

The number of particles 30 loaded into depots 28 may be controlled by controlling parameters such as, but not limited to, the pressure with which particles 30 are projected from particle source 36, the angle θ of particle source 36 relative to depot 28, the distance d_{psos} between particle source 36 and depot 28, the ratio of therapeutic substance to filler within particles 30, and the actual size of particles 30. The number of particles 30 that will fit into any given depot 28 is primarily a function of the size of particles 30. Generally, larger particles 30 do not pack together within a defined space as easily as smaller particles 30 do. As the size of particles 30 increases, more empty spaces are created within depot 28 in between particles 30. By contrast, smaller particles 30 can pack together more readily, thereby allowing more particles 30 to be loaded into depot 28.

Figure 7A depicts a portion of implantable device 10 that contains depot 28 within outer surface 20 and has been loaded with particles 30 as described above. During the process, some particles 30 enter depot 28 while other particles 30 may be deposited along surface 20. Particles 30 located on outer surface 20 but not within depot 28 may be removed to yield implantable device 10 having particles 30 loaded solely in depot 28 as depicted in Figure 7B.

Particles 30 may be removed from outer surface 20 using conventional techniques, such as, but not limited to, scraping, squeegeeing, or soaking. The scraping method involves the mechanical stripping of particles 30 from outer surface 20 using, for example, a brush. The squeegeeing method involves passing implantable device 10 through an opening in a sponge filled with cleaning solution containing liquids such as, but not limited to, water, ethanol, DMSO, or hexane. The soaking method involves soaking implantable device 10 in a cleaning

solution containing liquids such as, but not limited to, water, ethanol, DMSO, or hexane. The soaking method may or may not include sonication. Particular care should be taken during the removal of particles 30 from outer surface 20 such that particles 30 are not also removed from within depot 28.

c. Loading Particles into Depots and onto the Outer Surface of the Implantable Device

In some embodiments, loading of particles 30 is desired along outer surface 20 as well as within depots 28 of implantable device 10. In such embodiments, polymeric primer 38, with or without a therapeutic substance, is applied to outer surface 20 and depot 28 prior to the projection of particles 30 onto implantable device 10 to facilitate retention of particles 30 on outer surface 20 and within depot 28, as described above. The application of polymeric primer 38 is controlled such that depot 28 is not more than 50% filled with polymeric primer 38. The primed implantable device 10 is then loaded with particles 30 as described above. During the process, some particles 30 enter primed depot 28 while other particles 30 are deposited along primed outer surface 20. The particles 30 entering depot 28 as well as the particles 30 loaded onto outer surface 20 will adhere to and/or become embedded in primer 38, as depicted in Figure 8.

d. Use of Topcoats

In some embodiments, a polymeric topcoat 42, with or without a therapeutic substance therein, is deposited atop particles 30 loaded onto implantable device 10. Polymeric topcoat 42 can be applied by any conventional method, such as the immersion or spray techniques described above with reference to the application of polymeric primer 40. Polymeric topcoat 42 may be used to secure particles 30 to implantable device 10. Polymeric topcoat 42 also will typically reduce the rate of release of the substance or substances of which particles 30 are made from implantable device 10. Examples of suitable polymers were listed above, and such examples are equally applicable here. By way of example and not limitation, the polymeric topcoat 42 can have a thickness of about 0.25 microns to about 1.5 microns. Typically, topcoat 42 can have a thickness of about 1 micron. It will be appreciated by one of ordinary skill in the art that the thickness of the polymeric topcoat 42 is based on factors such as the type of procedure for which implantable device 10 is employed and the rate of release that is desired.

Figure 9A illustrates an embodiment in which polymeric topcoat 42 is applied and dried subsequent to the loading of particles 30 onto outer surface 20 of primered implantable device 10. Such an embodiment facilitates immobilization of particles 30 on outer surface 20 via primer 38 followed by the controlled release of the substance or substances of which particles 30 are made via topcoat 42.

Figures 9B, 9C, and 9D illustrate alternative embodiments in which topcoat 42 is applied to implantable device 10 having depots 28 formed therein. In Figure 9B, topcoat 42 is applied over particles 30 within depot 28. In Figure 9C, topcoat 42 is applied along outer surface 20, which has no particles 30 loaded thereon, as well as over particles 30 within depot 28. In Figure 9D, topcoat 42 is applied over particles 30 within depot 28 and over particles 30 along primered outer surface 20.

Methods of Use

As mentioned above, implantable devices that may be treated according to the methods of the present invention include stents and grafts, among other possibilities. An implanted stent or graft, having one or more substances loaded thereon as described above, is useful for treating occluded regions of blood vessels caused by thrombosis and/or restenosis, among other possible uses.

Stents may be placed in a wide array of blood vessels, both arteries and veins. Briefly, an angiography is first performed to determine the appropriate positioning for stent therapy. Angiography is typically accomplished by using a catheter to inject a radiopaque contrasting agent into an artery or vein as an X-ray is taken. A guidewire is then advanced through the lesion or proposed site of treatment. Over the guidewire is passed a delivery catheter which allows a stent in its collapsed configuration to be inserted into the passageway. The delivery catheter is inserted either percutaneously or by surgery into the femoral artery, brachial artery, femoral vein, or brachial vein and advanced into the appropriate blood vessel by steering the catheter through the vascular system under fluoroscopic guidance. A stent having the above described covering may then be expanded at the desired area of treatment. A post-insertion angiogram may also be utilized to confirm appropriate positioning.

Vascular grafts may be used to replace, bypass, or reinforce diseased or damaged sections of a vein or artery. The general procedure for implantation includes the step of pre-clotting, wherein the graft is immersed in the blood of the patient and allowed to stand for a period of time sufficient for clotting to ensue. After pre-clotting, hemorrhaging is less likely to occur when the graft is implanted, and thus the growth of tissue is not impeded. Grafts may be placed either through invasive surgery or non-invasively through percutaneous endoluminal transport. Percutaneous delivery of a graft avoids the complications and risks of surgery. The graft may be attached to the vessel at each end of the diseased region, thus bypassing the diseased region. Alternatively, the diseased region may be removed and replaced by the graft.

While particular embodiments and applications of the present invention have been shown and described, it will be apparent to those of ordinary skill in the art that changes and modifications can be made without departing from this invention in its broader aspects. Therefore, the appended claims are to encompass within their scope all such changes and modifications as fall within the true spirit and scope of this invention.

CLAIMS

What is claimed is:

1. A method of loading a therapeutic substance onto an implantable device, said method comprising:
projecting a dry stream of particles from a pressurized particle source onto a preselected region of said implantable device, said particles including a therapeutic substance.
2. An implantable device loaded with a therapeutic substance in accordance with the method of Claim 1.
3. The method of Claim 1, wherein said implantable device 10 is selected from a group of stents and grafts.
4. The method of Claim 1, wherein said therapeutic substance is selected from a group consisting of antineoplastic, antimitotic, antiinflammatory, antiplatelet, anticoagulant, antifibrin, antithrombin, antiproliferative, antibiotic, antioxidant, and antiallergic substances and combinations thereof.
5. The method of Claim 1, wherein said therapeutic substance is selected from a group consisting of radioactive isotopes and radiopaque substances.
6. The method of Claim 1, wherein said therapeutic substance is selected from a group consisting of bioabsorbable polymers, biomolecules, and biostable polymers.

7. The method of Claim 1, wherein said preselected region of said implantable device comprises the entire outer surface.

8. The method of Claim 1, wherein said preselected region of said implantable device comprises a middle section of said implantable device.

9. The method of Claim 1, wherein said preselected region of said implantable device comprises a portion of said implantable device adjacent an end of said implantable device.

10. The method of Claim 1, wherein an outer surface of said implantable device has a plurality of depots formed therein, wherein said preselected region of said implantable device comprises a portion of said outer surface having said plurality of depots formed therein, and wherein said particles are loaded onto said portion of said outer surface and within said plurality of depots.

11. The method of Claim 10, wherein said method additionally comprises the act of:
removing said particles from said portion of said outer surface, wherein said particles remain within said plurality of depots.

12. The method of Claim 1, wherein said pressurized source is operated at a pressure in the range between 10 PSI and 60 PSI.

13. The method of Claim 1, wherein prior to said act of projecting particles, the method further comprises the act of:
applying a polymeric primer to said preselected region of said implantable device.

14. The method of Claim 13, wherein said particles are projected so as to become embedded within said polymeric primer.

15. The method of Claim 1, the method further comprising:
applying a polymeric topcoat disposed on at least a portion of said particles on said preselected region of said implantable device.

16. A method of loading a therapeutic substance onto a stent having an outer surface having a plurality of depots formed therein, said method comprising:
projecting a dry stream of particles from a pressurized source onto said outer surface of said stent, so that said particles are loaded into said plurality of depots, said particles including a therapeutic substance.

17. A stent loaded with a therapeutic substance in accordance with the method of Claim 16.

18. The method of Claim 17, wherein said particles are projected so as to be loaded onto said outer surface.

19. The method of Claim 18, additionally comprising the act of:
removing said particles from said outer surface of said stent, wherein said particles remain within said plurality of depots.

20. The method of Claim 18, wherein prior to said act of projecting particles, the method further comprises the act of:
applying a polymeric primer to said outer surface and within said depot, wherein said particles are retained on said primer following said act of projecting particles.

21. The method of Claim 16, the method further comprising:
applying a polymeric topcoat disposed on at least a portion of said particles on said stent.

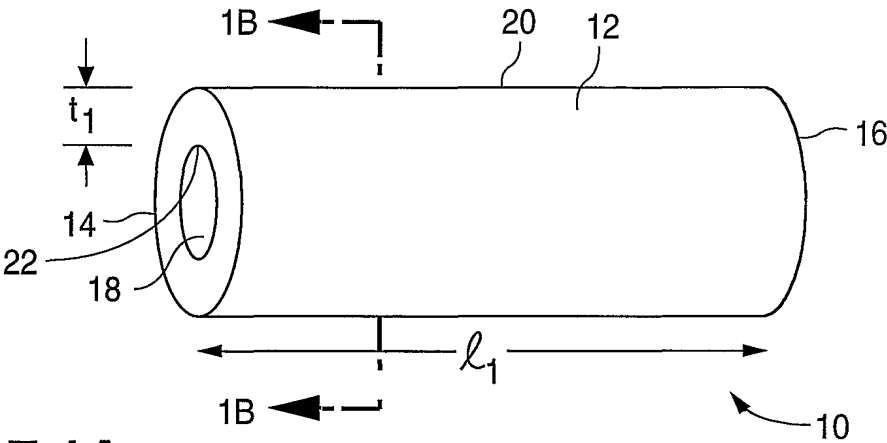


FIGURE 1A

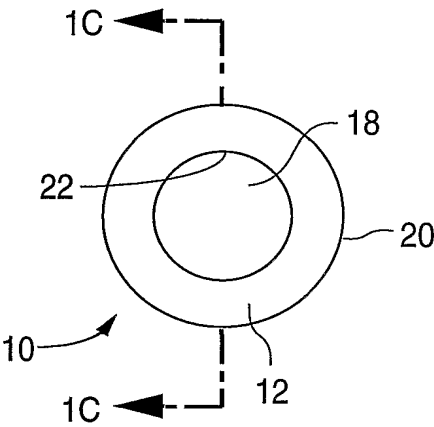


FIGURE 1B

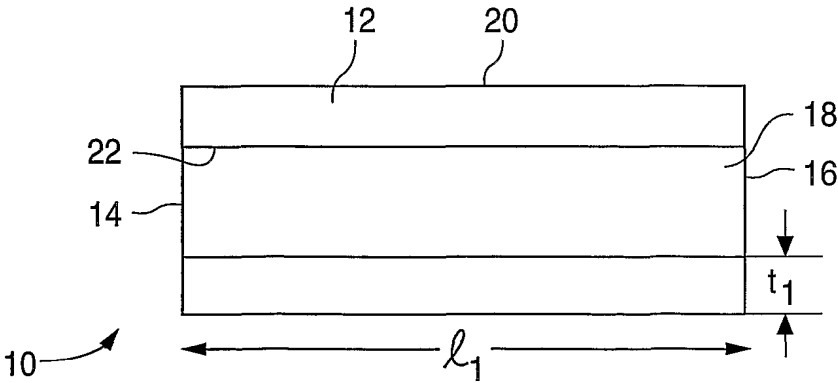


FIGURE 1C

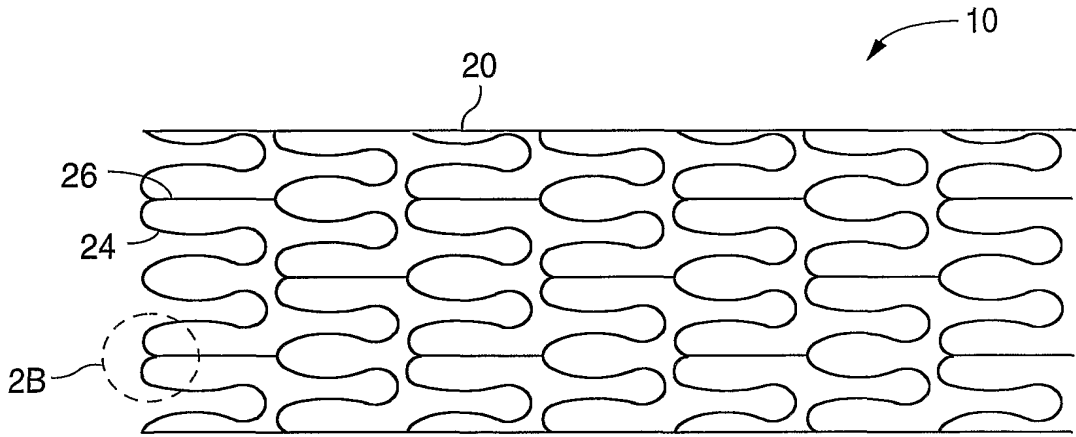


FIGURE 2A

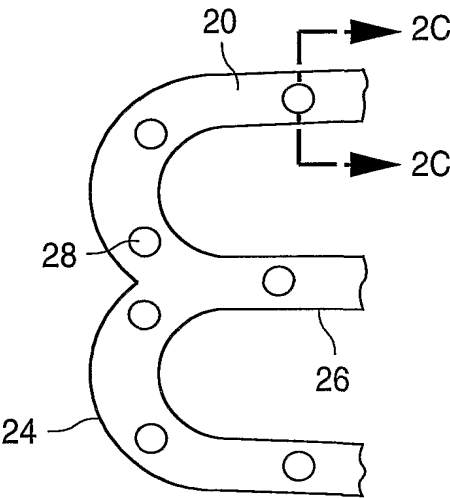


FIGURE 2B

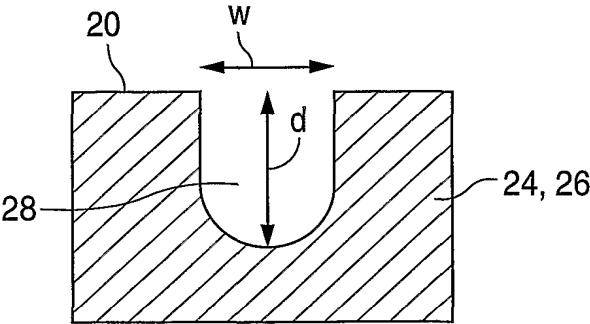


FIGURE 2C

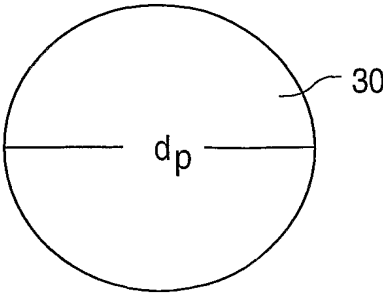


FIGURE 3

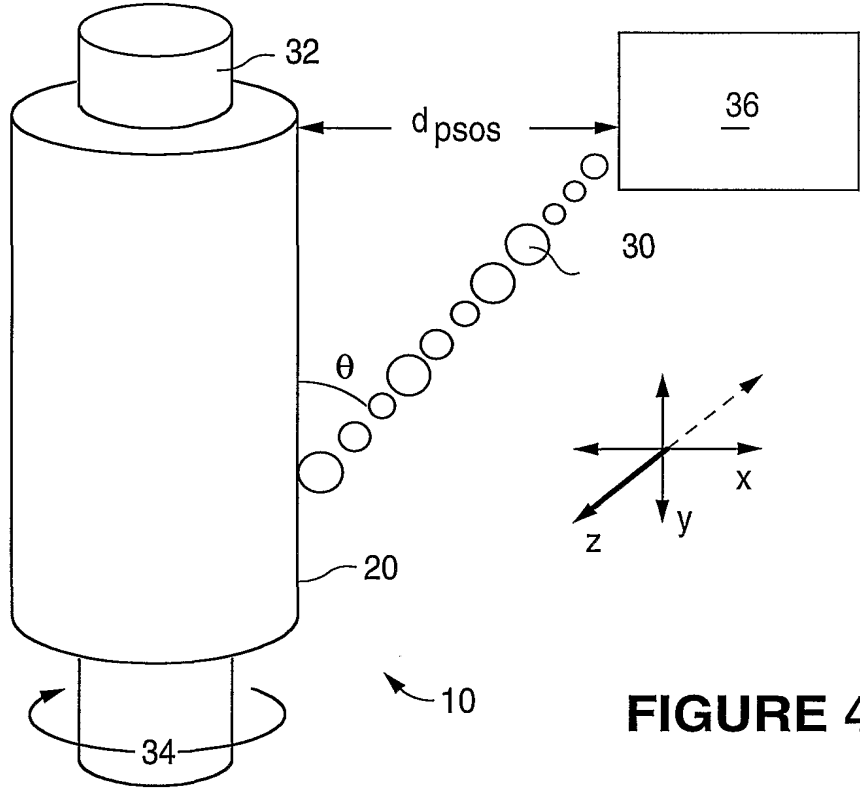


FIGURE 4

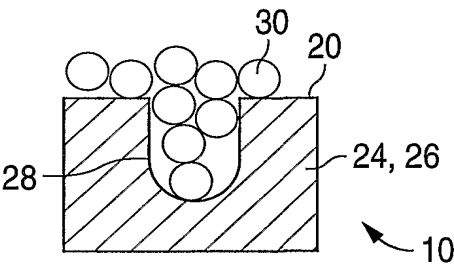


FIGURE 7A

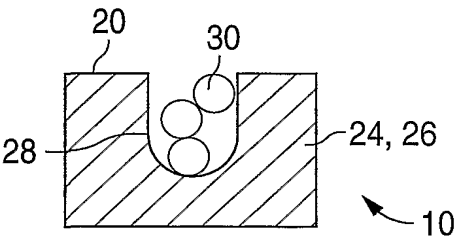


FIGURE 7B

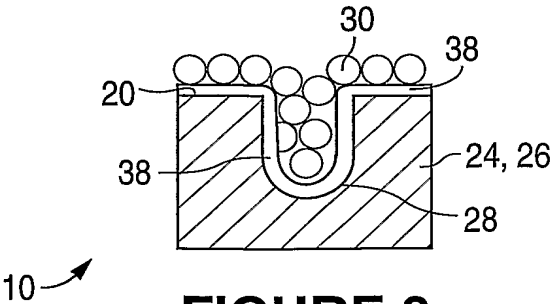


FIGURE 8

4/6

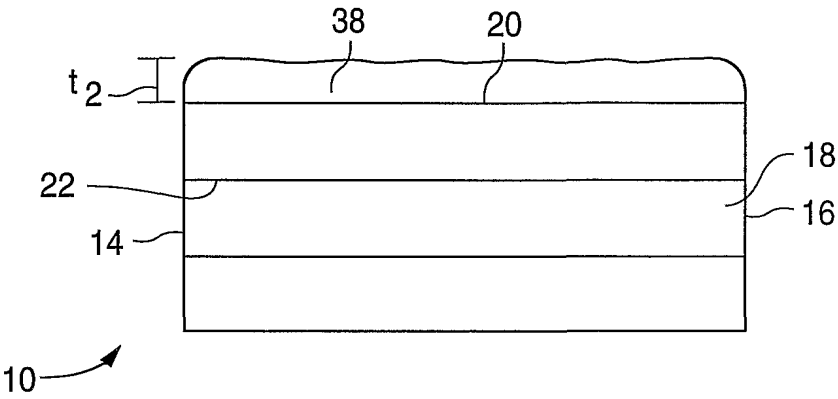


FIGURE 5A

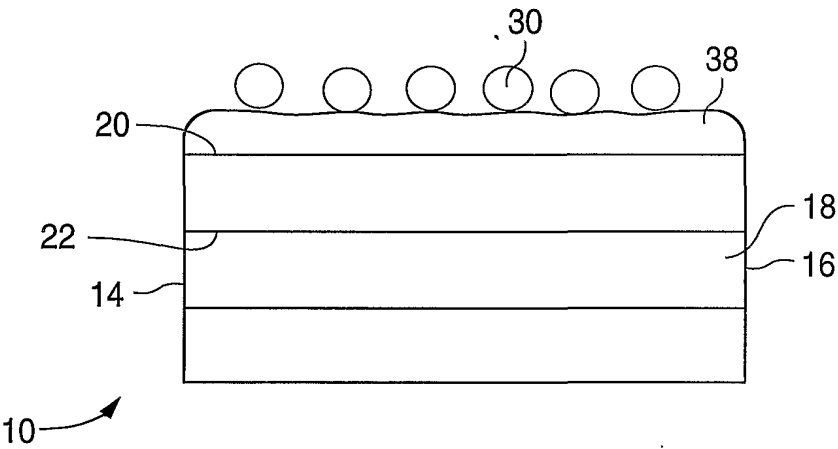


FIGURE 5B

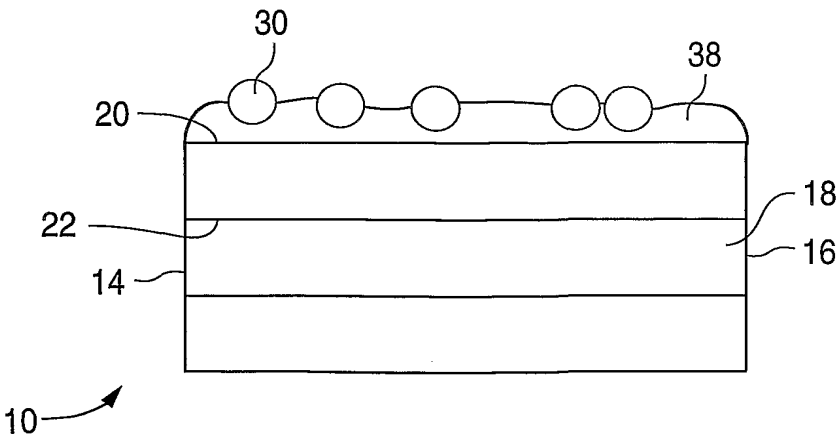


FIGURE 5C

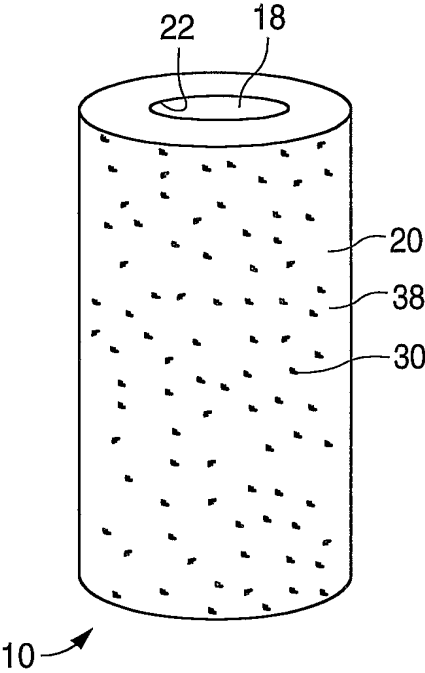


FIGURE 6A

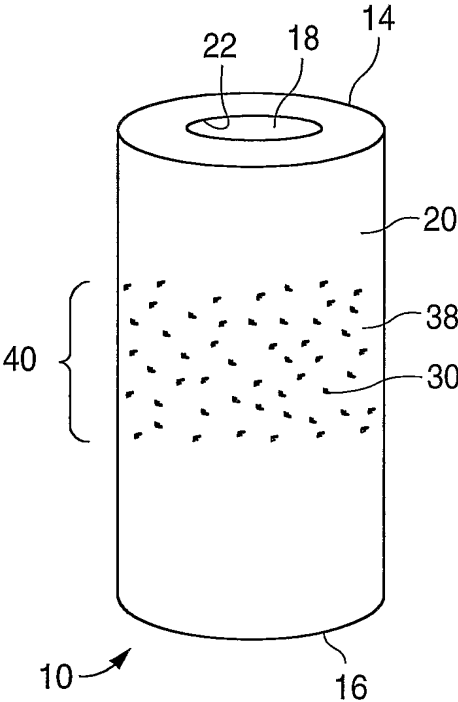


FIGURE 6B

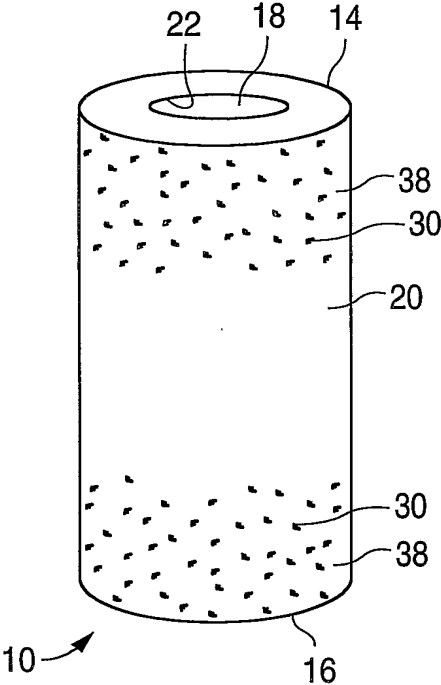
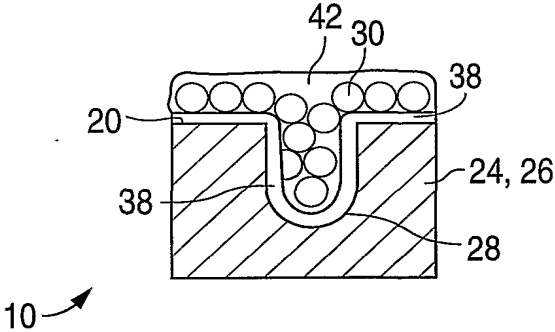
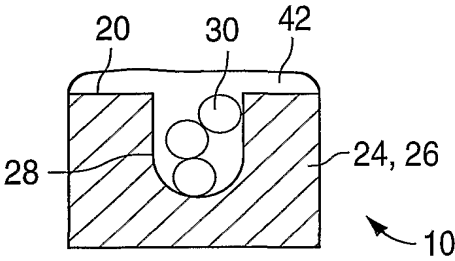
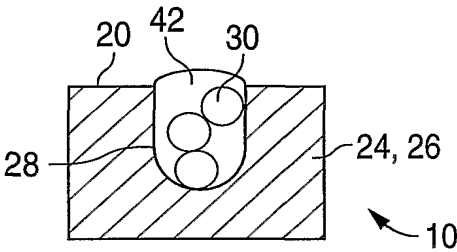
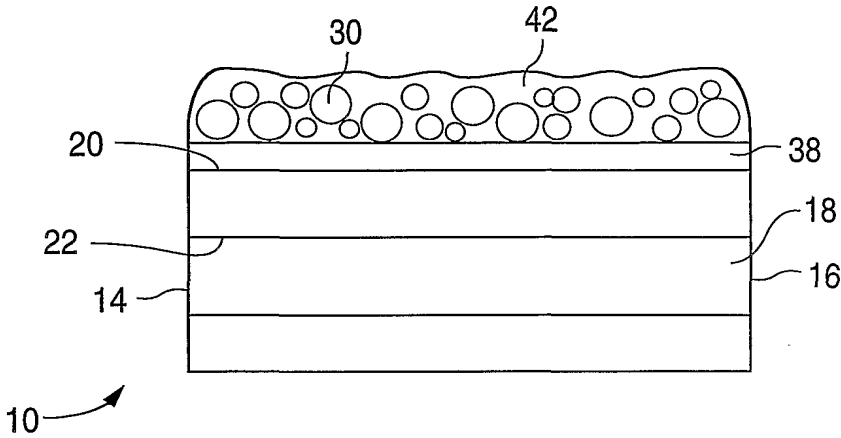


FIGURE 6C



(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
4 April 2002 (04.04.2002)

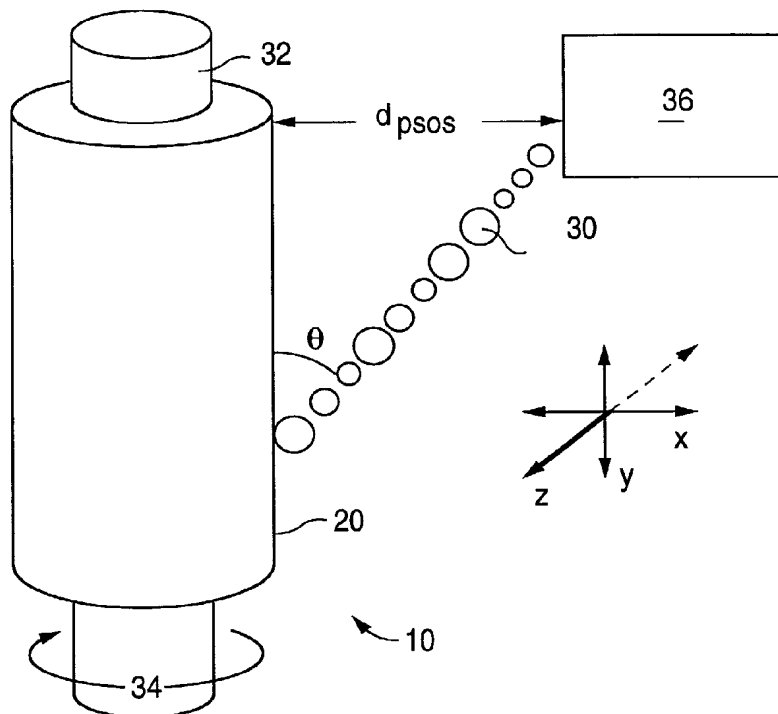
PCT

(10) International Publication Number
WO 02/026162 A3

- (51) International Patent Classification⁷: **A61F 2/06**
- (21) International Application Number: PCT/US01/27627
- (22) International Filing Date:
5 September 2001 (05.09.2001)
- (25) Filing Language: English
- (26) Publication Language: English
- (30) Priority Data:
09/671,759 26 September 2000 (26.09.2000) US
- (71) Applicant: **ADVANCED CARDIOVASCULAR SYSTEMS, INC.** [US/US]; 3200 Lakeside Drive, Santa Clara, CA 95054 (US).
- (72) Inventors: **HARISH, Sameer**; 43505 Ocaso Corte, Fremont, CA 94539 (US). **WU, Steven, Z.**; 2299 Lenox Place, Santa Clara, CA 95054 (US).
- (74) Agents: **KERRIGAN, Cameron et al.**; Squire, Sanders & Dempsey, L.L.P., 600 Hansen Way, Palo Alto, CA 94304-1043 (US).
- (81) Designated States (*national*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, UZ, VN, YU, ZA, ZW.
- (84) Designated States (*regional*): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

[Continued on next page]

(54) Title: A METHOD OF LOADING A SUBSTANCE ONTO AN IMPLANTABLE DEVICE



(57) Abstract: Methods of loading a substance onto an implantable device are disclosed. The implantable device may be a stent or a graft, with or without depots formed within an outer surface thereof. An exemplary method includes the act of projecting particles of the substance from a pressurized particle source onto a preselected region of the implantable device. An implantable device loaded with a substance in accordance with the method is also provided. The projected particles may be made of any substance or substances suitable for loading onto an implantable device in solid form including, but not limited to, therapeutic substances or agents, radioisotopes, radiopaque substances, polymers, proteins, and nucleic acids. Also provided is a method of loading a substance onto a stent having an outer surface with a plurality of depots formed therein. The method includes the act of projecting particles including the substance from a pressurized particle source onto the outer surface of the stent, wherein the particles are loaded into the plurality of depots. A stent loaded with a substance in

accordance with the method is also provided.



WO 02/026162 A3



Published:

— with international search report

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(88) Date of publication of the international search report:

16 January 2003

INTERNATIONAL SEARCH REPORT

Inter al Application No

PCT/US 01/27627

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 A61F2/06

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 A61F A61L

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

WPI Data, EPO-Internal

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	US 6 096 070 A (RAGHEB ET AL) 1 August 2000 (2000-08-01) the whole document -----	1-10, 16, 17



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- *&* document member of the same patent family

Date of the actual completion of the international search

30 July 2002

Date of mailing of the international search report

05/08/2002

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Smith, C

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

PCT/US 01/27627

Patent document cited in search report		Publication date	Patent family member(s)	Publication date
US 6096070	A	01-08-2000	US 5609629 A	11-03-1997
			AU 716005 B2	17-02-2000
			AU 5588896 A	19-12-1996
			CA 2178541 A1	08-12-1996
			WO 9817331 A1	30-04-1998
			US 5824049 A	20-10-1998
			US 5873904 A	23-02-1999
			EP 0747069 A2	11-12-1996
			JP 9099056 A	15-04-1997
